DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

PHILADELPHIA DISTRICT
M2857

900 U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106

Telephone: 215-597-4390

WARNING LETTER

August 10, 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ravi V. Desphande, President
Bio-Pharm, Inc.
10 H Runway Drive
Levittown, PA 19057

Dear Mr. Desphande:

From March 31 through June 14, 1999, Food and Drug Administration (FDA) Investigator Edward D. McDonald and Compliance Officer James C. Illuminati conducted an inspection of Bio-Pharm, Inc., located in Levittown, Pennsylvania. During this inspection deviations from Current Good Manufacturing Practices (CGMP) regulations codified as Title 21 Code of Federal Regulations (21 CFR) Part 211 were documented. The inspection revealed that drug products manufactured at your facility are adulterated under Section 501(a)(2)(B) of the Food, Drug, and Cosmetic Act (the Act) in that the methods used in or the facilities or controls used for their manufacture, processing, packing, or holding do not conform to the CGMP regulations as described in 21 CFR Part 211.

These CGMP deviations were outlined on Form FDA 483, Inspectional Observations (copy attached) dated June 14, 1999, and were presented and discussed with you and Jay Doshi, Vice President, at the conclusion of the inspection. We are in receipt of your letter dated June 30, 1999 in response to the observations listed on the FDA 483. The observations represent serious violations of the Federal Food, Drug, and Cosmetic Act, as described below. We have included comments with respect to your response in the areas where we continue to have concerns, as follows:

1. The purified water system is not validated in that:

   A. Since 10/7/98 the water system has failed to meet the U.S.P. requirement for Total Organic Carbon (TOC) [redacted] times. During that period of time, [redacted] human drug products, including [redacted] pediatric products were distributed which

were manufactured and distributed with water that failed to meet the USP TOC requirement.

B. TOC testing, as required by the U.S.P., was not performed from 5/98 through 9/98. A total of [redacted] human drug products, which required purified water as a raw material, were manufactured during this time period.

C. The water system was not revalidated when the existing 254 nm UV lamp was replaced with a 185 nm UV lamp.

Your response to Observation #1 does not address the impact of the out-of-specification (OOS) TOC results obtained for purified water used in the manufacture of your pharmaceutical drug products. Your firm did not investigate these OOS TOC results and cannot provide scientific data regarding the identification of the contaminants causing the OOS TOC results. As a result, safety issues relative to such contaminants cannot be addressed because of the lack of a follow-up investigation.

We recognize that you continued to use the U.S.P. test for Oxidizable Substances and obtained satisfactory results for your water. However, the fact remains that you continued to manufacture human drugs with an OOS specification raw material and made no attempt to correct the problem.

2. The response appears to adequately address the observation.

3. ErgoCaff-PB Suppositories Lot [redacted] manufactured 6/5/98 failed the assay for the active ingredient Alkaloids of Belladonna with a result of [redacted] of declared (specification [redacted]) and was released. The lot also failed in-process testing bulk top [redacted] and bulk bottom [redacted] for Alkaloids of Belladonna.

We agree with you that you need an OOS Standard Operating Procedure (SOP) and the necessity to investigate such results. However, your response fails to address the fact that a human drug product was released which failed the potency specification for an active ingredient (Alkaloids of Belladonna). The OOS SOP provides little or no detail regarding retesting. The retesting section of the SOP should be very detailed regarding the specific course of action to be pursued when an OOS event is encountered. We have noted the statement, "[redacted] in the SOP. We believe this statement leaves open the possibility that averaging of results may be used in some circumstances.

Averaging of passing and failing analytical results to obtain passing results is not an acceptable practice.

4. Equipment maintenance is not adequate in that during the manufacturing of Bisacodyl Suppositories, just prior to filling, a small green paint chip was found in [redacted] filling vessel [redacted] Peeling paint was also observed on [redacted] mixer [redacted] and homomixer [redacted]. This equipment is used in the manufacture of all suppository products.

We noted the corrective action taken with respect to this equipment prior to the close of the inspection. Production equipment inspection and maintenance is an ongoing responsibility of the firm and incidents such as this should not have to be brought your attention during an FDA inspection. Your firm needs to take a more aggressive approach regarding equipment cleaning and maintenance and needs to be more diligent with respect to the inspection of equipment prior to manufacturing operations.

A similar situation was documented during our 1996 inspection when our investigator observed foreign debris floating on top of finished acetaminophen solution, lot [redacted] stored in vessel [redacted].

5. There is no cleaning validation for Biodec DM Infant Drops. The firm has 10 different liquid finished products which use the same manufacturing and filling equipment.

The response fails to address cleaning validation with respect to all liquid drug products your firm manufactures.

6-11. The response appears to adequately address these observations.

12. HPLC analytical methods used to perform stability testing for ErgoCaff-PB Suppositories and Biodec DM Drops are not stability indicating in that the firm has not performed testing to assure that degradants related to the active ingredients in these products do not interfere with the analysis of each active ingredient in each respective product. Since these methods are also used for the assay of these products, there is no assurance that HPLC assay peaks for active ingredients in ErgoCaff-PB Suppositories and Biodec DM Drops are free from interferences from degradants related to active ingredients and excipients.

Your response addresses only analytical methodology for ErgoCaff-PB Suppositories and Biodec DM Drops. Analytical methodology

used for stability testing for all drug products manufactured by your firm should be reviewed and validated if necessary to assure that degradants and excipients do not interfere with the analysis of the active ingredients. We would expect you to set up a program and timetable to review the assay and stability methods which you are currently using for your products.

13-19. The response appears to adequately address these observations.

The above is not intended to be an all-inclusive list of deficiencies that exist at your firm. FDA inspections are audits which are not intended to determine all deviations from CGMPs. It is not the role of FDA to inspect a firm into compliance. As top management, it is your responsibility to ensure that all requirements of the CGMP regulations are being met as well as all other requirements of the Act. The specific violations noted in this letter and in the FDA 483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems.

Review of the FDA 483 dated June 17, 1996 (copy attached) issued at the close of the prior FDA inspection of your firm reveals a number of observations including, incomplete validation of your purified water system, use of analytical methods for stability testing which were not stability indicating, and use of an unvalidated assay method for Biotapp Elixir, which were again observed during our recent inspection. Be assured that the adequacy of the corrective actions you have taken to bring your firm into compliance with the regulations will be reviewed carefully during the next Food and Drug Administration inspection of your firm.

You should take prompt action to correct the deviations with respect to all products where these deficiencies in controls apply. Failure to promptly take corrective action may result in regulatory action without further notice. Possible regulatory actions include seizure and/or injunction.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. Additionally, new drug applications (NDA's), abbreviated new drug applications (ANDA's), and export approval requests may not be approved until the aforementioned violations are corrected.

Please advise this office in writing within fifteen (15) days of receipt of this letter as to any additional specific actions you have taken or intend to take to correct these violations and prevent their recurrence. Your reply should be directed to the attention of James C. Illuminati, Compliance Officer, at the address referenced above.

Sincerely,

Thomas D. Gardine

Thomas D. Gardine
District Director
Philadelphia District

Enclosure: As stated

cc: Division of Primary Care and Home Health Services
PA Department of Health
P. O. Box 90
Harrisburg, PA 17120